

Remarks

Applicants have amended the paragraph at page 7, line 29 of the original specification to recite the presence of Figures 9A-9C and to recite sequence identifiers. Applicants have amended the paragraph at page 9, lines 22-30 of the original specification to correct typographical errors. Support for the recitation of IGFBP-5 is found at least in the first complete paragraph on page 15 of the original specification.

Applicants have canceled claims 1-22 and 28-31 without prejudice to Applicants' rights to pursue their subject matter in the present application and in other applications. Applicants have amended claim 23 to recite a pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2), wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6. Support for the amendment is found in the original application at least in Examples 2, 3, and 6-8. Claims 24 and 25 have been amended to comport with amended claim 23.

Applicants have added new claims 32-34. Support for new claim 32 is found in the original application at least in original claims 23 and 26. Support for new claims 33 and 34 are found in the original application at least in original claims 24 and 25, respectively.

Applicants submit that the amendments introduce no new matter into the application.

Upon entry of this paper, claims 23-27 and 32-34 will be pending and presented for examination.

Objection to the Specification

The Office action objected to the specification because the brief description of the drawings referred to "Figure 9" rather than "Figures 9A to 9C" and because the brief description of the drawings did not include sequence identifiers. Applicants have amended the brief description of the drawings accordingly and request withdrawal of the objection.

35 U.S.C. § 112

The Office action rejected claims 23-27 as allegedly failing to comply with the enablement requirement. Applicants request withdrawal of the rejection.

Claims 23-27 are drawn to pharmaceutical compositions, which the Office has construed to be compositions used for the purpose of treating a disease. The Office action does not appear to dispute that the application enables molecules which dissociate a protein complex comprising an IGF and an IGFBP. Rather, the Office action appears to argue that the application does not show that a compound which dissociates a protein complex comprising an IGF and an IGFBP “can be used for treating any kind of disease” and therefore does not enable a pharmaceutical composition comprising such a molecule, as testing whether the compound can be used for treating a disease would allegedly constitute undue experimentation.

Applicants submit that the application does indeed enable pharmaceutical compositions. The application discusses in some detail (see, for example, pages 51-54) how to formulate and administer pharmaceutical compositions. Thus, the application teaches how to make and how to use the claimed invention. This is sufficient to comply with the enablement requirement of 35 U.S.C. § 112; Applicants therefore request that the rejection be reconsidered and withdrawn.

Applicants understand that the Office action questions whether the pharmaceutical composition would in fact be useful to treat any disease. The application, however, reports that IGFs are therapeutically useful (see, *e.g.*, the experiment disclosed at page 64 of the application; see also page 5 of the application, discussing the efficacy of IGF-I with respect to hypoxic-ischemic brain injury and age-related changes in NMDA receptor subtype and the age-related decline in both working and reference memory and cell proliferation in the dentate gyrus). The present application demonstrates the elevation of IGFBP-2 gene expression in fibroblasts from subjects with major depression (Example 2); the slight elevation of IGFBP-2 gene expression in brain tissue from subjects with major depression (Example 3); and the effects on IGFBP-2 gene expression of drugs possessing anxiolytic and antidepressant properties (Example 6). Applicants submit that, based on the high level of skill in the art, the specific guidance in the application and the knowledge in the art, any experimentation to confirm the effectiveness of the disclosed and

enabled pharmaceutical compositions of the invention which dissociate an IGF from an IGFBP such as IGFBP2 would be routine and not undue.

Applicants also note that the enablement of the present application was confirmed by a paper published after the priority date of the present application and before the actual filing date of the present application. Applicants enclose as IDS reference C1 a copy of Mackay *et al.* (2003 Oct) J. Cereb. Blood Flow Metab. 23(10):1160-7, reporting that “administration of NBI-31772 at the time of ischemia onset also dose-dependently reduced infarct size, and the highest dose (100 microg) significantly reduced both total (by 40%, $P<0.01$) and cortical (by 43%, $P<0.05$) infarct volume” in one model and, in another model “reduced both cortical infarct volume (by 40%, $P<0.01$) and brain swelling (by 24%, $P<0.05$), and it was still effective when treatment was delayed up to 3 hours after the induction of ischemia” (Mackay, abstract).

Applicants therefore request withdrawal of the rejection.

35 U.S.C. 102

The Office action rejected claims 23-27 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,428,781 (“Sakano”).

Applicants have amended claim 23 to recite a pharmaceutical composition which dissociates a protein complex comprising IGF and IGFBP-2, *wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6.* Sakano does not appear to teach such a composition. Applicants therefore request withdrawal of the rejection of claims 23-27.

New claims 32-34 relate to pharmaceutical compositions which dissociate a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), wherein the composition is a small molecule. Sakano does not teach such a pharmaceutical composition. The Office action appears to allege that the proteins of Sakano, such as “[Leu27, Leu43]rIGF-II or one of anti-IGFBP antibodies” are small molecules.

Proteins are not small molecules. See, *e.g.*, Schreiber (2005) Nature Chemical Biol. 1(2):64-66, a copy of which is enclosed as IDS reference C2: “What are small molecules? We know best what they are not-- nature's DNA, RNA, and protein macromolecules residing within

their cellular contexts.” See also

www.genomicglossaries.com/content/drug_discovery_gloss.asp:

small molecule therapeutics: Low molecular-weight drug. Compared to larger molecular weight pharmaceuticals such as proteins, peptides, and carbohydrates, small molecules can more easily penetrate cell membranes and the blood brain barrier. Can be delivered orally or intravenously. These molecules tend to incur lower process development and manufacturing costs. [CHI RNA Therapeutics report , 2002] (emphasis added)

Thus, proteins are not small molecules. Accordingly, the proteins of Sakano cannot anticipate claims 32-34.

Applicants request reconsideration and withdrawal of the rejection.

Conclusion

Upon entry of this paper, claims 23-27 and 32-34 will be pending and presented for examination. Applicants respectfully request the issuance of a notice of allowance.

Examiner Lu is invited to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,



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